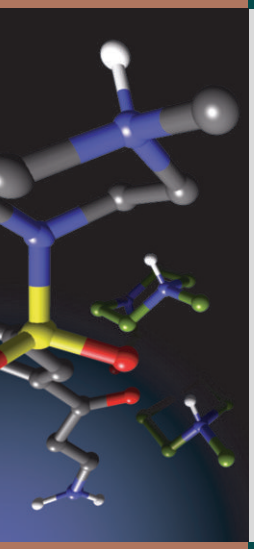


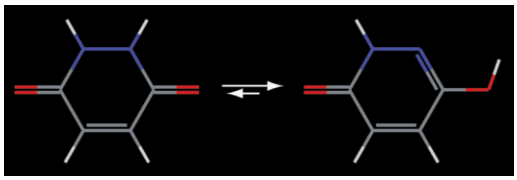
Epik

Rapid and robust pK_a predictions

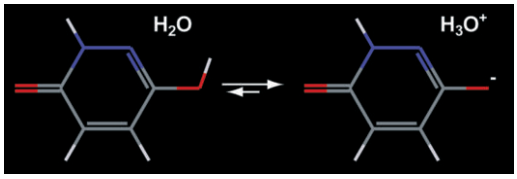
Combining the proven reliability of Hammett and Taft methods with powerful tautomerization tools, Epik is the program of choice for accurate enumeration of ligand protonation states in physiological conditions.

SCHRÖDINGER®

The Advantages of Empirical pK_a Prediction



Maleic hydrazide is commonly represented as a dione. However, this dione tautomerizes to form an alcohol *(above)*. The alcohol is subsequently deprotonated in water *(below)*. Because Epik iteratively tautomerizes and ionizes, it is able to correctly identify this acidic hydrogen and return a deprotonated output structure.

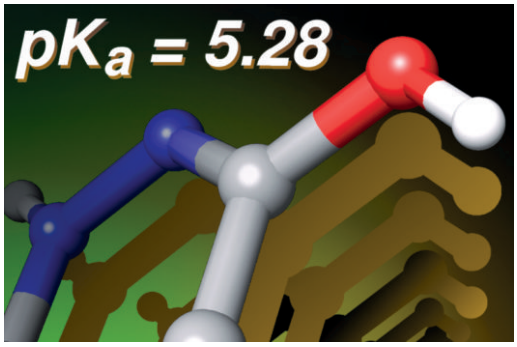


Proper treatment of ligand protonation states is essential to lead discovery. The pK_a values of a drug's various functional groups play a critical role in determining its bioavailability and pharmacokinetic profile, while virtual screening software relies on correctly protonated structures in order to perceive the discrete interactions that drive ligand binding. However, many readily available libraries provide ligand structures in familiar tautomeric forms with all functional groups neutralized. These forms may not be highly populated under physiological conditions, and are therefore inappropriate for property prediction or virtual screening experiments.

Epik provides a time-tested solution to these problems, designed specifically to work within the context of contemporary drug discovery workflows. Using Hammett and Taft methods in conjunction with ionization and tautomerization tools, Epik is able to rapidly and reliably predict pK_a values and return all chemically sensible structures.

Epik: Maximizing Returns in Lead Discovery

Epik predicts the pK_a of maleic hydrazide to be 5.28, which is in good agreement with the experimentally determined pK_a of 5.67.



Epik is designed to bring accuracy and efficiency to the lead discovery pipeline, eliminating time wasted on incorrect protonation states. Its features include:

- **Support for multiple output structures:** While other software may only be capable of returning a single structure or pK_a value, Epik can return pK_a values and 3D structure files for multiple tautomers and ionization states that are likely to exist under the specified conditions.
- **Tautomeric optimization:** Epik is distinguished by its ability to treat tautomeric states without user intervention, an invaluable feature when processing millions of ligands.
- **Multiple solvent choices:** Epik is parametrized to return accurate pK_a values in both water and DMSO.
- **Multiple prediction modes:** For maximum speed, Epik can predict pK_a values for a structure file in its supplied state. For maximum accuracy, Epik can vary the tautomeric and ionization states if necessary.
- **LigPrep integration:** With a single click, Epik can automatically be employed by LigPrep to enumerate tautomers and protonation states.
- **Easy-to-use interface:** A streamlined standalone interface makes it effortless to set up calculations and interpret results.
- **Cross-platform support:** Epik calculations can run on Linux, SGI, and AIX machines, and features distributed processing to expedite predictions for large numbers of compounds.

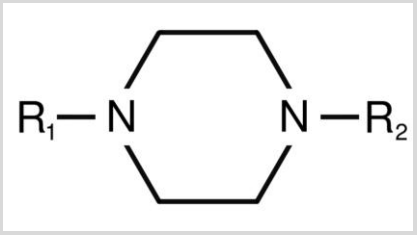
Performance-Driven Technology

2-pyridone, a relatively common heterocycle, is frequently represented as 2-hydroxypyridine (shown in the background), but it exists primarily in the tautomeric state illustrated in the foreground. Supplied with either form of 2-pyradone, Epik returns both tautomers and correctly identifies the more prevalent of the two.

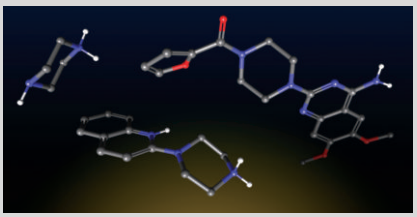
Epik is built upon a solid scientific foundation designed to accurately model a wide range of chemical functionalities under real-world conditions:

- **Hammett and Taft methodology:** Epik predicts pK_a values using the well-established Hammett and Taft approaches, empirical methods in which a functional group's pK_a is amplified or attenuated according to both the type and presence of adjoining moieties. Epik has been parametrized using a broad data set, and returns accurate results in both water and DMSO.
- **Structural iteration:** Because tautomerization and ionization affect the pK_a values of functional groups throughout a ligand, Epik uses an iterative algorithm for maximum accuracy. This algorithm first tautomerizes the starting structure, and then ionizes the tautomers accordingly. The resulting set of new structures is then re-tautomerized and re-ionized up to four additional times or until the cycle converges.
- **Efficient calculations:** At maximum speed, Epik calculations allow structure libraries to be processed at a rate of considerably less than one second per ligand.
- **Penalty calculation:** Epik can calculate a penalty term that denotes the prevalence of any given output structure. This structure-associated penalty term can be applied at later steps in the drug discovery pipeline — for example, when post-processing or evaluating virtual screening results.
- **Uncertainty prediction:** To assist researchers in assessing the calculated predictions, Epik reports the standard deviation for each pK_a value.

Accurate Treatment of Drugs and Drug-like Molecules



Epik correctly handles piperazine rings in a variety of chemical environments. Above, the 2D structure of the piperazine moieity. Below, 3D structures of piperazine, quipazine, and prazosin after protonation state adjustments by Epik.



The piperazine moiety (shown at left as a 2D structure) is commonly found in drugs and drug-like molecules, and in its simplest form (R1, R2 = H) is a pharmaceutical agent used to treat parasitic infections. However, in spite of its ubiquitous nature, this functionality is mistreated by some ionization tools, which incorrectly protonate both nitrogen atoms.

Epik correctly predicts the protonation state of piperazine rings that occur in a variety of chemical environments. In the case of prazosin, an alpha-adrenergic blocker used to treat hyptertension, the nitrogen lone pairs are delocalized across the R1 and R2 substituents, and Epik protonates neither piperazine nitrogen under physiological conditions. In the serotonergic agonist quipazine, one of the piperazine nitrogen atoms is bonded to an aromatic ring system. Consequently, the two piperazine nitrogens have significantly different proton affinities, and only one of them is protonated. Epik predicts the pK_a of this quipazine species to be 8.75, in excellent agreement with the experimentally determined pK_a of 8.82.

Evaluation Copies

To request an evaluation copy of Epik, please contact info@schrodinger.com. Our staff of support scientists will be happy to assist you in giving Epik a thorough trial.

Epik

Rapid and robust pK_a predictions

System Requirements:

LINUX
- Pentium or better
- Linux kernel 2.4 (Red Hat 7.3) or later
- 256 MB memory

SGI
- R5000 or better
- IRIX 6.5.2m or later
- 256 MB memory

IBM AIX
- Power series or better
- AIX 4.3.3 or AIX 5.x
- 256 MB memory

A Coordinated Family of Products

Epik is a versatile tool for predicting pK_a values, ionization states, and tautomers, and is designed to be useful as part of a broader drug discovery workflow. Epik is an ideal complement to the following software:

- **Glide:** High-throughput ligand-receptor docking for fast library screening
- **Phase:** A high-performance program for ligand-based drug design
- **LigPrep:** Rapid 2D to 3D structure conversion

All Schrödinger products are seamlessly integrated through the Maestro graphical interface.

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